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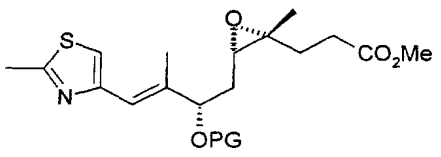
(54) Title: PROCESS FOR THE PRODUCTION OF EPOTHIOLONE B AND DERIVATIVES AS WELL AS INTERMEDIATE PRODUCTS FOR THIS PROCESS



(II)

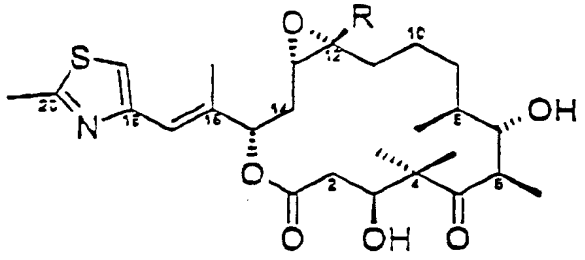
(57) Abstract: The present invention is directed to a process for the production of epothilone compounds, the improvement comprising preparing said compounds by cyclization of a compound produced from an intermediate of formula (II) wherein PG is a protecting group.

Process for the Production of Epothiolone B and Derivatives as well as Intermediate Products for this Process

This application claims the benefit of the filing date of U.S. Provisional Application Serial No. 60/145,005, filed July 22, 1999.

This invention relates to a process for the production of epothilone B and derivatives as well as intermediate products for this process.

It is known that the natural substances epothilone A (R = H) and epothilone B (R = methyl) (compound I, DE 195 42 986 A1, DE 41 38 042 C2)



(I)

R = H, CH_3

have a fungicidal and cytotoxic effect. According to indications for in vitro activity against mammary and intestinal tumor cell lines, this family of compounds appears especially advantageous for the development of a pharmaceutical agent. Various working groups have successfully endeavored to synthesize these macrocyclic compounds. In this connection, the working groups start from various fragments of the macrocycle to synthesize the desired natural substances.

In any case, diastereomer-pure fragments as starting products and intermediate products are required for a successful epothilone synthesis. Diastereomer purity is often decisive for

the action and reliability of a pharmaceutical agent and thus a requirement for its production.

The total synthesis of epothilone A is described by Schinzer et al. in Chem. Eur. J. 1996, 2, No. 11, 1477-1482 and in Angew. Chem. 1997, 109, No. 5, pp. 543-544).

Epothilone derivatives were already described by Höfle et al. in WO 97/19086. These derivatives were produced starting from natural epothilone A or B.

Another synthesis of epothilone and epothilone derivatives was described by Nicolaou et al. in Angew. Chem. 1997, 109, No. 1/2, pp. 170-172. Nicolaou et al. also described the synthesis of epothilone A and B and several epothilone analogs in Nature, Vol. 387, 1997, pp. 268-272, and the synthesis of epothilone A and its derivatives in J. Am. Chem. Soc., Vol. 119, No. 34, 1997, pp. 7960-7973 as well as the synthesis of epothilone A and B and several epothilone analogs in J. Am. Chem. Soc., Vol. 119, No. 34, 1997, pp. 7974-7991.

Nicolaou et al. also describe in Angew. Chem. 1997, 109, No. 19, pp. 2181-2187 the production of epothilone A analogs using combinative solid-phase synthesis. Several epothilone B analogs are also described there.

A variable synthesis for the production of epothilone and different types of derivatives is known from WO 99/07692.

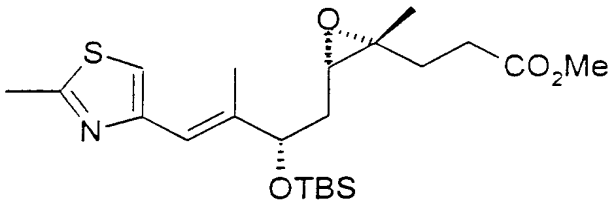
Other syntheses are described in PCT Applications WO 99/02514 and WO 99/01124.

Finally, the epothilone B-synthesis that is described by J. Mulzer et al. in Tetrahedron Letters 39 (1998) 8633-8636 can also be mentioned.

Because of the expected lability of the epoxide, in all previous syntheses of epothilone B, the corresponding (Z)-olefin was always epoxidated in the last step, whereby the diastereosection is 4:1 to 20:1 of the desired ß-isomer.

An object of this invention is to indicate a process for the production of epothilone B and epothilone B derivatives, in which the cis-epoxide is introduced at a considerably earlier time via dihydroxylation-monosulfonation of a suitable (E)-olefin, whereby the ß-configuration of the cis-epoxide is to come from the previous dihydroxylation. Other object are evident to one of ordinary skill.

These objects are achieved by a process using a compound of formula II



II

in which TBS stands for a tributylsilyl group. Instead of TBS, another suitable protective group can also be another suitable protective group can also be used as a starting compound, in which the epoxy group of the epothilone is already contained, and whereby this epoxy group remains unchanged in all subsequent reaction steps up to the end product.

Diagram 3 shows possible derivatizations that allow for the process according to the invention if compound 11 that is to be used and/or next steps 13 or 14 are modified as indicated. This invention therefore extends not only to the process for the production of epothilone B, but also to a process for the production of correspondingly modified derivatives that are derived from modified compounds 11, 13 or 14.

In addition, the invention also relates to the compounds of formulas 5 to 21, which are all new, as well as the correspondingly modified derivatives, which are obtained in the procedures indicated above and in diagram 3.

The selection of protective group (PG) in the 15-hydroxy group can be made with only routine experimentation. PG should outlast all subsequent reactions up to the macrolactonization, but in addition should also be removable in the presence of epoxide. The original TBS-function may not be removed without destroying the substrate; however, after converting the 15-OTBS derivative into the 15-OTES analog (TES = triethylsilyl), any additional synthesis step can be performed easily. Other suitable groups can be routinely determined TBS is preferably replaced by TES at steps 13, 14 or 15; at steps 15 and 17-19, PG is preferably TES.

The epoxide applied early thus was shown as stable under the following reaction conditions:

1. Reduction (neutral (DIBAH), ionic (selectride), metallic (Zn)
2. Oxidation (osmium tetroxide-sodium periodate)
3. Bases (fluoride in an aprotic solvent, DMAP, LDA, enolate). In this case, it is especially surprising

that C- and O-anions that were produced intramolecularly at a 1,5-interval to the epoxidic centers do not open the epoxide nucleophilically.

4. Electrophiles (acylation with acid chloride in the Yamaguchi reaction).

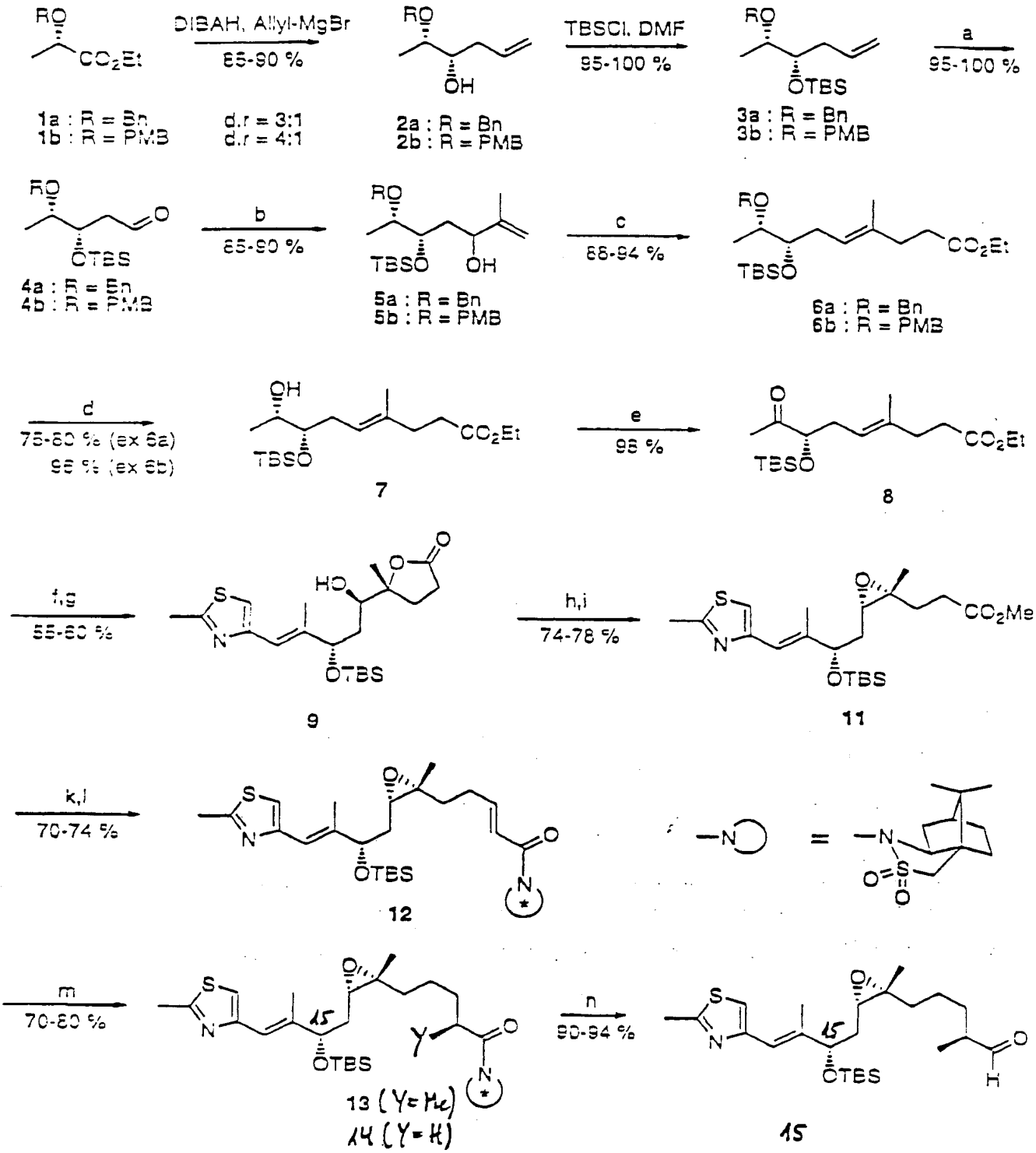
Of all the reagents used, only aqueous acid led to epoxide opening. Apart from the mechanistically valuable finding that does away with the preconception that epoxides are in any case highly reactive synthesis intermediate compounds, the early epoxide introduction also has considerable advantages for the production according to the invention of epothilone B and the corresponding derivatives:

The N-oxide formation on thiazole that is observed in the 12,13-epoxidation with peracid develops just like the separation of the 12,13-epimeric epoxide. No "false" epoxide is produced. The stereoselection of the aldol reaction is also considerably higher than for the 12,13-(Z)-olefin analogs of 21.

The examples that are tied to diagram 3 are used for a more detailed explanation of the invention.

Diagram 1

Synthesis of the Completely Functionalized C15-C7-Fragments of Epothilone B

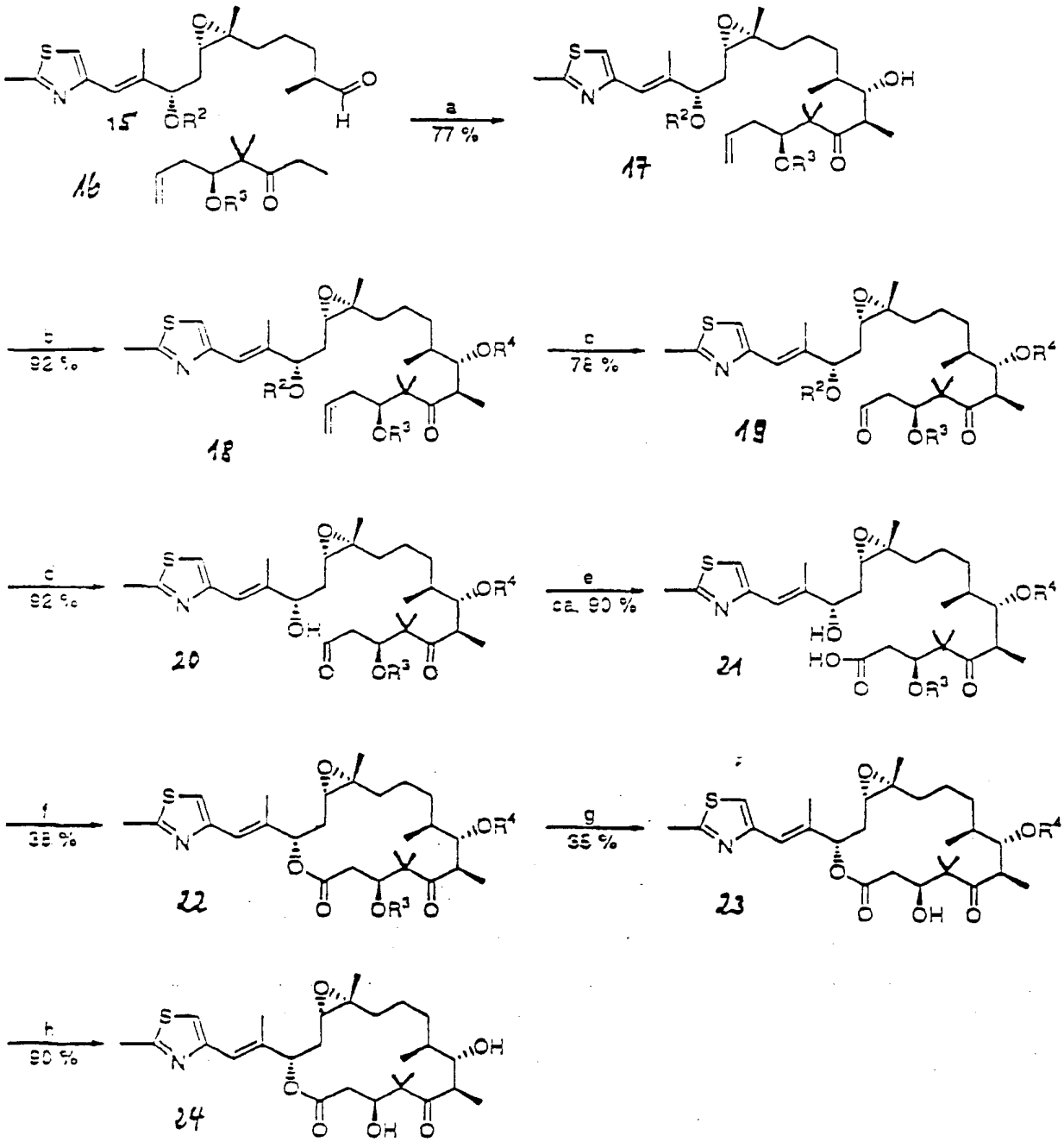


a) O_3, CH_2Cl_2, -78°C, PPh_3; b) isopropenyl-MgBr, THF, -10°C; c) $CH_3C(OEt)_3$, xylene, 120°C, 12 h; d) DDQ, CH_2Cl_2-H_2O, rt; e) Dess-Martin periodinane, CH_2Cl_2, rt, 12 h; f) AD-mix-ß, tBuOH-H_2O, rt, 20 h; g) Thz-CH_2-PBu_3Cl, KHMDS -78°C then 30°C; h) MsCl, NEt_3, CH_2Cl_2, 0°C, 30 min; i) K_2CO_3, MeOH, rt, 45 min; k) DIBAH, CH_2Cl_2, -90°C, 1 h; l) LiOH (in-situ), $(EtO)_2POCH_2CO(N°)$, then aldehyde, Et_2O-THF, rt, 30 min; m) L-selectrides, THF -78°C, 1 h, then HMPA, mel, -78°C to 0°C, 4 h; n) DIBAH, CH_2Cl_2, -80°C to -70°C, 2 h.

Bn = benzyl; PMB = p-methoxy-benzyl. All selectrides (cf. Aldrich Chemical Catalog) can be used in the process. L-selectride (lithium-tri-sec-butylborohydride) is preferred.

Diagram 2

Total Synthesis of Epothilone B (Epoxide Path)

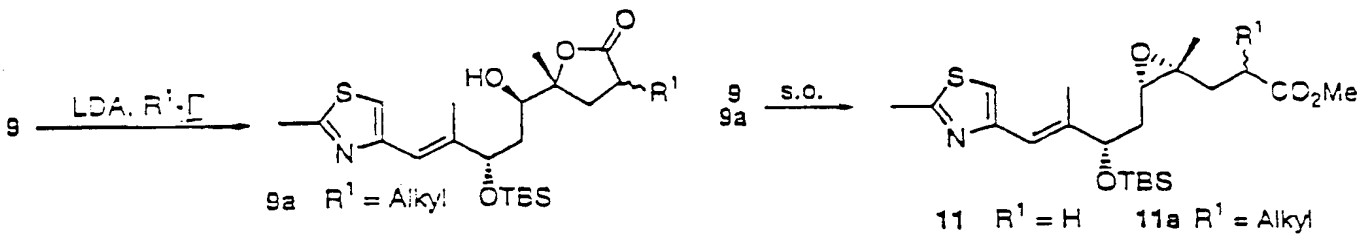


a) LDA, THF, -78°C; b) TrocCl, pyridine, CH_2Cl_2, rt; c) i. OsO_4, NMO; ii) $NaIO_4$; d) HF-Py, pyridine rt; e) $NaClO_2$, NaH_2PO_4, tBuOH, 2,3-dimethyl-2-butene; f) 2,4,6-trichlorobenzoyl chloride, NEt_3, then DMAP, toluene; g) HF-Py, pyridine rt; h) Zn, NH_4Cl, EtOH, reflux, 30 min.

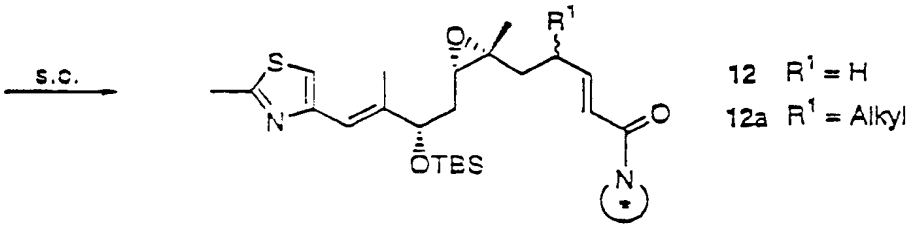
Ketone 16 K.C. Nicolaou et al.: **J. Am. Chem. Soc. 1997**, 119, 7974-7991

Diagram 3

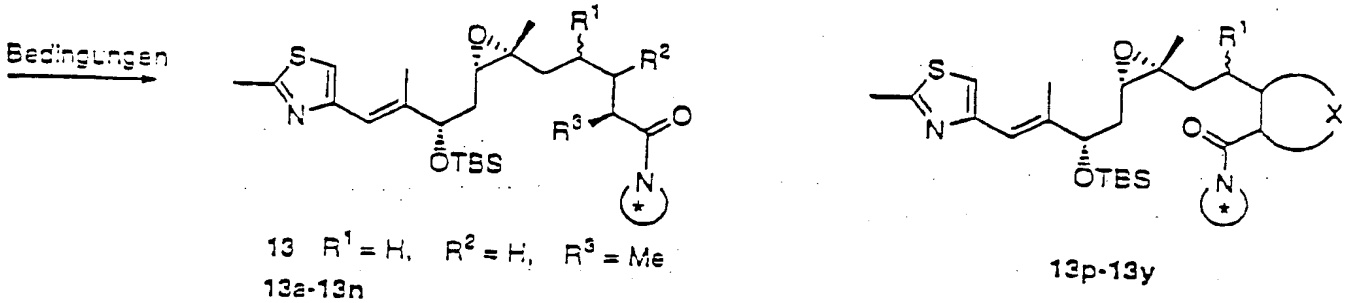
Derivatizations



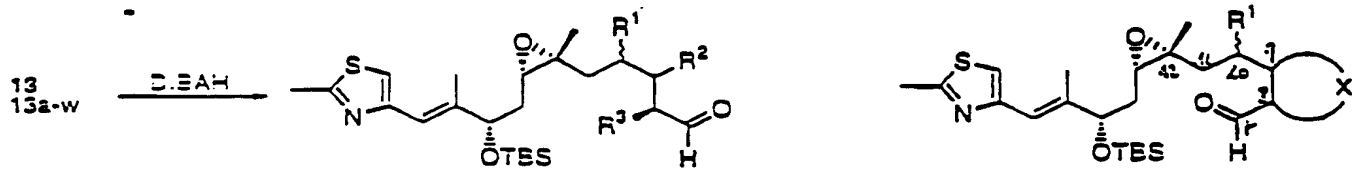
see above



Conditions



Products	Conditions	Products	Conditions
13a R^1 = H, R^2 = H, R^3 = H,	L-Selectrides, NH_4Cl	**13p** R^1 = H, X = CH2	CH_2N_2, $Pd(OAc)_2$
13b R^1 = H, R^2 = Alkyl, R^3 = H	$(R^4)_2CuLi$, NH_4Cl	**13q** R^1 = Alkyl, X = CH2	
13c R^1 = H, R^2 = H, R^3 = Alkyl	L-Selectride , R^3-I	**13r** R^1 = H, X = O	TBHP, EuLi odor
13d R^1 = H, R^2 = Alkyl, R^3 = Alkyl	$(R^4)_2CuLi$, R^3-I	**13s** R^1 = Alkyl, X = O	mCPBA
13e R^1 = Alkyl, R^2 = H, R^3 = H	L-Selectrides, NH_4Cl	**13t** R^1 = H, X = N-Alkyl	MeONHR, NaOMe
13f R^1 = Alkyl, R^2 = Alkyl, R^3 = H	$(R^4)_2CuLi$, NH_4Cl	**13u** R^1 = Alkyl, X = N-Alkyl	odor-N-Aminophtalimide
13g R^1 = Alkyl, R^2 = H, R^3 = Alkyl	L-Selectrides, R^3-I		$Pb(OAc)_4$
13h R^1 = Alkyl, R^2 = Alkyl, R^3 = Alkyl	$(R^4)_2CuLi$, R^3-I	**13v** R^1 = H, X = RCHCH=CHCHR'	Diels-Alder- reaction
13i R^1 = H, R^2 = Aryl, R^3 = H	Aryl-MgBr, NH_4Cl	**13w** R^1 = Alkyl, X = RCHCH=CHCHR'	R—R'
13k R^1 = H, R^2 = Aryl, R^3 = Alkyl	Aryl-MgBr, R^3-I		
13m R^1 = Alkyl, R^2 = Aryl, R^3 = H	Aryl-MgBr, NH_4Cl		
13n R^1 = Alkyl, R^2 = Aryl, R^3 = Alkyl	Aryl-MgBr, R^3-I	**13x** R^1 = H, **13y** R^1 = Alkyl X =	



Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius; and, unless otherwise indicated, all parts and percentages are by weight.

The entire disclosure of all applications, patents and publications, cited above, and U.S. Provisional Application Serial No. 60,145,005, filed July 22, 1999 is hereby incorporated by reference.

EXAMPLES

Experimental

$C_{18}H_{30}O_3Si$
Exact Mass: 322.1964
Mol. Wt.: 322.51
C, 67.03; H, 9.38

8.02 g (25 mmol) of alkene 3a is dissolved in 200 ml of absolute methylene chloride and mixed with 10 ml of absolute MeOH. After cooling to -78°C, a dried ozone/air mixture is introduced via a gas feed frit until the blue coloring begins. Air is allowed to blow through for two more minutes and then quenched by the addition of 19.67 g (75 mmol) of PPh_3 in portions, and it is allowed to thaw overnight. The solvent is removed as completely as possible in Rotavapor, and the remaining solid residue with use of preparative column chromatography (hexane/ethyl acetate/methylene chloride = 40:1:1) for separation of PPh_3, then Hx/EE 20:1 to 10:1. 7.90 g (98%) of aldehyde 4a is obtained as a colorless liquid.

^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (dd, J = 1.5, 2.0 Hz, 1H); 7.34-7.24 (m, 5H), 4.58 (d, J = 11.8 Hz, 1H), 4.45 (d, J = 11.8 Hz, 1H), 4.31 (dt, J = 6.3, 4.5 Hz, 1H), 3.58-3.51 (m, 1H), 2.69-2.62 (m, 1H), 2.51-2.43 (m, 1H), 1.14 (d, J = 6.3 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 201.8, 138.4, 128.4, 127.6, 71.0, 68.9, 46.0, 25.7, 17.9, 13.5, -4.7, -4.9.

IR (Film): ν_{max} 2956, 2857, 2712, 1730, 1472, 1255, 1102, 837, 778 cm^{-1}.

$C_{21}H_{36}O_3Si$
Exact Mass: 364.2434
Mol. Wt.: 364.5942
C, 69.18; H, 9.95; O, 13.16; Si, 7.70

75 ml of isopropenylmagnesium bromide (0.5 M, THF) and 25 ml of absolute THF are cooled to -10°C under Ar atmosphere, and 9.14 g (28.3 mmol) of aldehyde 4a (dissolved in 20 ml of absolute THF) is slowly (about 20 minutes) added in drops at -10°C. It is allowed to thaw to 0°C within 45 minutes (TLC monitoring, Grignard optionally must also be added), the reaction mixture is poured into 150 ml of semi-saturated NH_4Cl solution and shaken out after 120 ml of ether is added. The aqueous phase is extracted twice more with ether (100 ml). The combined organic phases are dried ($MgSO_4$), and the solvent is removed in Rotavapor. Preparative column chromatography (Hx/EE = 10:1) yields 9.48 g (92%) of allyl alcohol 5a (diastereomer mixture) as a colorless, viscous liquid.

Diastereomer 1

^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 4.98 (s, 1H), 4.80 (s, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.17 (d_{br}, J = 9.5 Hz, 1H), 4.02 (dt, J = 7.4, 4.5 Hz, 1H), 3.61-3.54 (m, 1H), 2.71 (d_{br}, J = 3.5 Hz, 1H), 1.84-1.75 (m, 1H), 1.72 (s, 3H), 1.65-1.57 (m, 1H), 1.14 (d, J = 6.5 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), -0.02 (s, 3H).

Diastereomer 2

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 4.99 (s, 1H), 4.83 (s, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.20 (dd, J = 8.0, 3.5 Hz, 1H), 3.90 (dt, J = 8.5, 4.3 Hz, 1H), 3.47 (dq, J = 6.4, 4.3 Hz, 1H), 2.97 (s_{br}, 1H), 1.86 (dt, J = 14.2, 4.1 Hz, 1H), 1.67 (s, 3H), 1.57 (dt, J = 14.6, 8.5 Hz, 1H), 1.10 (d, J = 6.4 Hz, 3H), 0.80 (s, 9H)

5a 6a

$C_{25}H_{42}O_4Si$
Exact Mass: 434.2852
Mol. Wt.: 434.6841
C, 69.08; H, 9.74; O, 14.72; Si, 6.46

8.02 g (22 mmol) of allyl alcohol 5a (diastereomer mixture) is dissolved in 120 ml of absolute xylene and mixed with 32 ml (176 mmol) of triethylorthoacetate and 4 drops of propionic acid. With a light Ar stream through a thin capillary, it is stirred for 16-20 hours at 120°C, whereby the ethanol that is produced is distilled off via a small distillation apparatus. After the reaction is completed (TLC monitoring), the solvent is distilled off in Rotavapor (30 mbar, 50°C, then complete vacuum), and the crude product is purified by column chromatography (Hx/EE = 40:1 gradient 20:1). 8.77 g (92%) of 6a is obtained as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (m, 5H); 5.20 (t, J = 6.4 Hz, 1H); 4.57 (d, J = 12 Hz, 1H), 4.48 (d, J = 12 Hz, 1H),

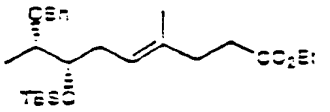
4.11 (q, J = 7.2, 2H), 3.68 (m, J = 4 Hz, 1H), 3.46 (dt, J = 6.3, 4.5 Hz, 1H), 2.40-2.34 (m, 1H), 2.32-2.24 (m, 2H), 2.14-2.04 (m, 1H), 1.60 (s, 3H), 1.23 (t, J = 7.2 Hz, 2H), 1.11 (d, J = 6.4 Hz, 3H), 0.84 (s, 9H), -0.02 (s, 3H), -0.05 (s, 3H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 173.5, 139.1, 134.5, 128.2, 127.5, 127.4, 124.0, 122.4, 77.3, 74.0, 71.0, 60.2, 34.8, 33.1, 30.1, 25.8, 18.0, 16.1, 14.2, 14.0, -4.60, -4.61.

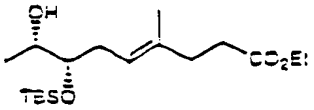
IR (Film): ν_{max} 2956, 2930, 2887, 2857, 1737, 1472, 1462, 1454, 1370, 1300, 1255, 1155, 1098, 939, 836, 776, 737 cm^{-1}.

HRMS (EI) Cld. for $C_{25}H_{42}O_4Si$ 434.2852, Fnd. 434.2845

$[\alpha]^{20}_D$ = -3.9 (c = 1.2. $CHCl_3$)



6a



7

$C_{18}H_{36}O_4Si$
Exact Mass: 344.2383
Mol. Wt.: 344.5515
C, 62.74; H, 10.53; O, 18.57; Si, 8.15

912 mg (2.10 mmol) of 6a is dissolved in 40 ml of methylene chloride and 2 ml of water, mixed with 2.86 g (12.6 mmol) of DDQ and stirred vigorously for exactly 3 hours at room temperature. The reaction mixture is diluted with 100 ml of ether and washed with $NaHCO_3$ (aqueous, saturated) (2x 40 ml). The combined aqueous phases are diluted with 80 ml of water and extracted with ether (2x 50 ml). The combined organic phases are washed with brine (50 ml), dried ($MgSO_4$), and the solvent is removed in

Rotavapor. Preparative column chromatography (Hx/EE = 10:1) yields 575 mg (80%) of alcohol 7 as a colorless liquid.

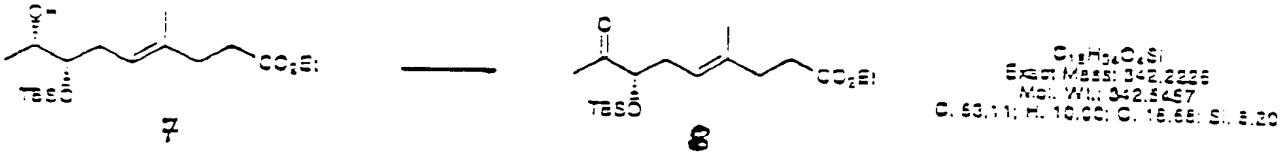
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (dt, J = 7.3, 1.0 Hz, 1H), 4.09 (q, J = 7.07 Hz, 2H), 3.56 (m, 1H), 3.42 (dt, J = 7.2, 4.4 Hz, 1H), 2.40-2.26 (m, 5H), 2.15-2.07 (m, 2H), 1.61 (m, 3H), 1.23 (t, J = 7.0 Hz, 3H), 1.09 (d, J = 6.5 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 173.7, 136.1, 120.9, 77.0, 69.0, 60.7, 35.2, 33.5, 33.0, 26.2, 20.3, 18.5, 16.6, 14.6, -3.8, -4.3.

IR (Film): ν_{max} 3513 (br), 2932, 2874, 2855, 1738, 1463, 1372, 1255, 1157, 1088, 836, 777 cm^{-1}.

HRMS (EI) Cld. for ($M^+ - C_4H_9$) 287.168, Fnd. 287.168 ± 5 ppm

$[\alpha]^{20}_D$ = +20.2 (c = 1.08, $CHCl_3$)



1.030 g (2.99 mmol) of alcohol 7 is dissolved in 50 ml of absolute methylene chloride and mixed with 2.5 ml of absolute pyridine and 2.54 g (6.0 mmol) of Dess-Martin periodinane and stirred overnight at RT (about 18 hours). For working-up, it is mixed with 25 ml of sodium thiosulfate solution (20%, aqueous), and it is stirred vigorously for 15 minutes. The phases are separated, and the aqueous phase is extracted with methylene chloride (2 x 25 ml). The combined organic phases are dried

($MgSO_4$), and the solvent is removed in Rotavapor. Preparative column chromatography (Hx/EE = 10:1) yields 945 mg (92%) of ketone 8 as a colorless liquid.

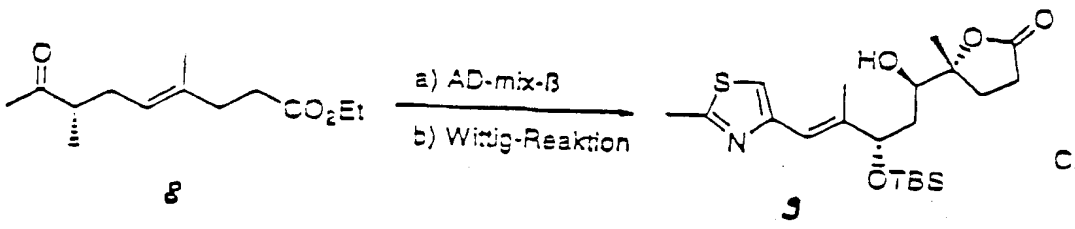
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (t, 1H, J = 6.8 Hz, 1H); 4.10 (q, J = 7.0 Hz, 2H), 3.97 (dd, J = 6.5, 5.5 Hz, 1H), 2.40-2.20 (m, 6H), 2.12 (s, 3H), 1.59 (s, 3H), 1.23 (t, J = 7.0 Hz, 1H), 0.89 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 212.5, 173.7, 137.0, 119.7, 79.2, 60.7, 35.1, 33.9, 33.7, 33.4, 26.1, 25.9, 18.5, 16.6, 14.6, -4.5, -4.6.

IR (Film): ν_{max} 2932, 2875, 2858, 1737, 1351, 1256, 1203, 1160, 1137, 1102, 959, 927, 899, 839, 779 cm^{-1}.

HRMS (EI) Cld. for (M^+-CH_3) 327.1992. Fnd. 327.199 ± 0.0016

$[\alpha]^{20}_D$ = -19.4 (c = 1.05, $CHCl_3$)



8 9

$C_{21}H_{39}NO_4SSi$
Exact Mass: 425,21
Mol. Wt.: 425,66
C, 59,26; H, 8,29; N, 3,29

a) 830 mg (2.42 mmol) of 8 is dissolved in 30 ml of $_t$BuOH-H_2O (1:1) and mixed with 1.5 g of $NaHCO_3$, 5.0 g of AD-Mix-ß and 230 mg of methanesulfonamide. After 36-48 hours at room temperature while being stirred vigorously, it is quenched by

adding 5 g of sodium sulfite (10 more minutes of stirring). After 25 ml of H_2O and 100 ml of methylene chloride are added, the phases are separated, and the aqueous phase is extracted with methylene chloride (3 x 30 ml). The combined organic phases are dried ($MgSO_4$), and the solvent is removed in Rotavapor. Preparative column chromatography (Hx/EE = 2:1, $R_{f\ (3:1)}$ = 0.09 to 0.29) yields 942 mg of product mixture 8a.

IR (Film): ν_{max} 3432, 2933, 2858, 1736, 1377, 1256, 1229, 1095, 837, 778 cm^{-1}.

b) 1.82 g of Wittig salt (5.2 mmol) is dissolved in 30 ml of absolute THF under Ar atmosphere, cooled to -78°C, and 10.4 ml of KHMDS (0.5 M, toluene) is added in drops and stirred for 45 minutes at -78°C. Then, 920 mg of 8a (dissolved in 2.5 ml of THF) is added smoothly in drops. It is allowed to stir for 5 more minutes at -78°C, the cooling bath is then quickly exchanged for an approximately 40°C water bath and allowed to thaw. After 5 minutes, the bath is removed, and it is allowed to stir for another 5 minutes before being quenched with 50 ml of NH_4Cl (saturated, aqueous) and 75 ml of ether. The aqueous phase is extracted with ether (2x 30 ml). The combined organic phases are dried ($MgSO_4$), and the solvent is removed in Rotavapor. Preparative column chromatography (Hx/EE = 2:1) yields 632 mg (61% on both synthesis steps) of alkene 9 as a colorless, viscous liquid.

^1H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.47 (s, 1H), 4.41 (dd, J = 8.5, 4.5 Hz, 1H), 3.67 (d, J = 10.0 Hz, 1H), 3.45 (s,

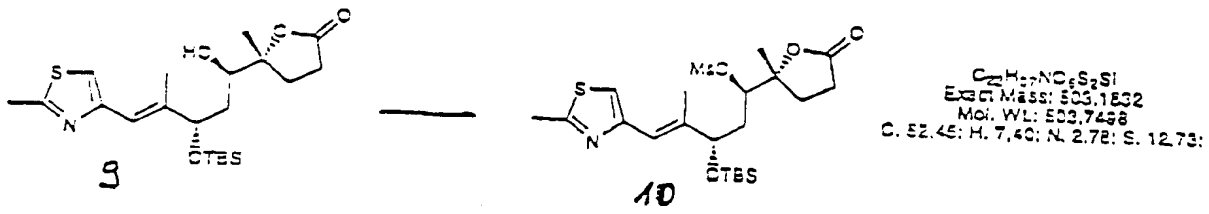
1H), 2.71-2.61 (m, 1H), 2.68 (s, 3H), 2.66-2.46 (m, 1H), 2.37-2.28 (m, 1H), 1.99 (s, 3H), 1.80-1.66 (m, 2H), 1.70 (dd, J = 14.3, 4.8 Hz, 1H), 1.34 (s, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 177.6, 165.1, 152.9, 141.4, 120.4, 116.3, 88.0, 79.9, 76.7, 37.1, 30.9, 29.9, 26.2, 23.6, 19.6, 18.4, 14.1, -4.0, -4.8.

IR (Film): ν_{max} 3469, 2955, 2943, 2930, 2910, 2892, 2856, 1768, 1656, 1505, 1462, 1386, 1252, 1066, 838 cm^{-1}.

HRMS (EI) Cld. for C21H35NO4SiS 425.2056 Fnd. 425,2060 ± 0.0025

$[\alpha]^{20}_D$ = -27.1 (c = 1.0, $CHCl_3$)

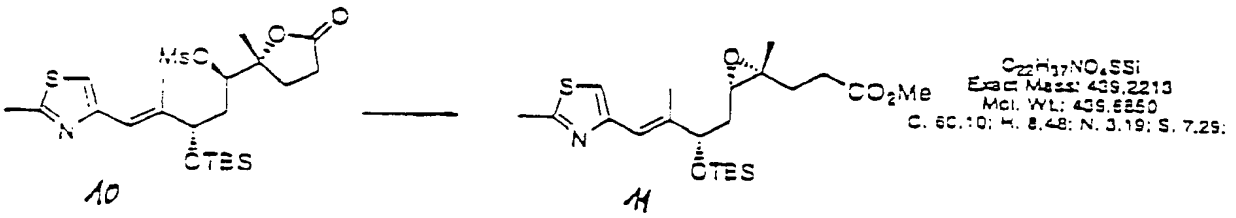


313 mg (0.737 mmol) of alcohol 9 is dissolved under Ar atmosphere in 5 ml of absolute methylene chloride and mixed at 0°C with 0.31 ml of absolute triethylamine and 0.09 ml of methanesulfonic acid chloride. After 30 minutes, it is quenched with 10 ml of $NaHCO_3$ (aqueous, saturated), the phases are separated, and the aqueous phase is extracted with methylene chloride (3x 10 ml). The combined organic phases are dried

($MgSO_4$), and the solvent is removed in Rotavapor. Preparative column chromatography (Hx/EE = 4:1) yields 283 mg (76%) of mesylate 10 as a strongly viscous, yellowish liquid.

^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.56 (s, 1H), 4.57 (dd, J = 8.0, 2.5 Hz, 1H), 4.41 (dd, J = 8.8, 4.8 Hz, 1H), 3.13 (s, 3H), 2.68 (s, 3H), 2.60-2.53 (m, 2H), 2.02 (d, J = 1.0 Hz, 3H), 2.07-1.81 (m, 4H), 1.42 (s, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 175.5, 165.0, 153.2, 138.7, 122.1, 117.2, 86.5, 83.8, 75.7, 39.6, 38.0, 31.2, 28.8, 26.2, 21.7, 19.7, 18.5, 13.1, -4.3, -4.6.



256 mg (0.508 mmol) of mesylate 10 is dissolved in 10 ml of absolute methanol and mixed with finely pulverized potassium carbonate. After 45 minutes at room temperature, it is diluted with 30 ml of ether and then filtered. Saturated NH_4Cl solution (15 ml) is added to the filtrate until two clear phases form. The phases are separated, and the aqueous phase is extracted with ether (3x 10 ml). The combined organic phases are dried ($MgSO_4$), and the solvent is removed in Rotavapor. Preparative column

chromatography (Hx/EE = 5:1) yields 202 mg (90%) of epoxide 11 as a colorless, viscous liquid.

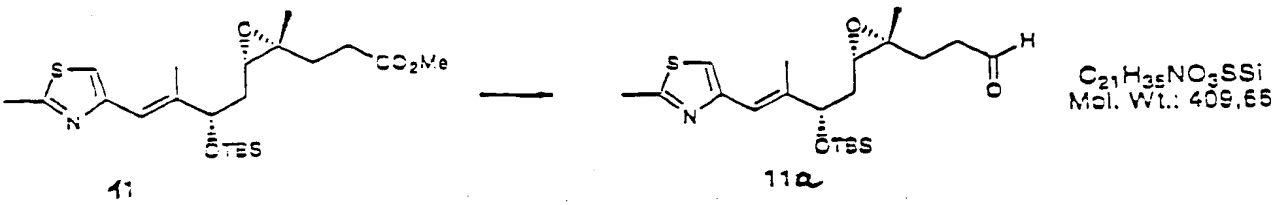
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.49 (s, 1H), 4.32 (dd, J = 9.0, 3.5 Hz, 1H), 3.65 (s, 3H), 2.89 (dd, J = 7.0, 4.5 Hz, 1H), 2.68 (s, 3H), 2.46-2.40 (m, 2H), 1.99 (d, J = 1.5 Hz, 1H), 1.94-1.77 (m, 3H), 1.63-1.55 (m, 1H), 1.26 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 173.6, 164.9, 153.4, 142.4, 119.3, 115.8, 76.7, 62.8, 60.4, 52.1, 36.3, 30.5, 28.6, 26.3, 22.5, 19.6, 18.6, 14.4, -4.2, -4.7.

IR (Film): ν_{max} 2955, 2874, 2857, 1740, 1656, 1505, 1439, 1380, 1312, 1230, 1180, 1077, 835, 778 cm^{-1}.

HRMS (EI) Cld. for $C_{22}H_{37}NO_4SiS$ 439.2213 Fnd. 439.221 ± 0.0025.

$[\alpha]^{20}_D$ = -12.6 (c = 1.04, $CHCl_3$)



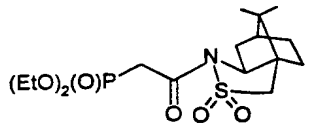
11 11a

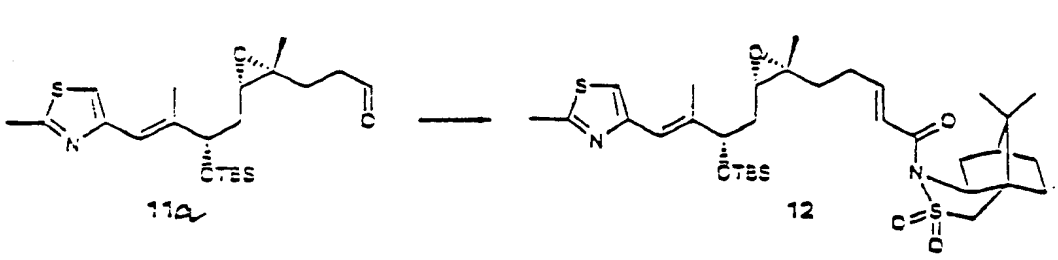
$C_{21}H_{35}NO_3SSi$
Mol. Wt.: 409.65

176 mg (0.40 mmol) of epoxide 11 is dissolved in 6 ml of absolute MC under argon and slowly (about 5 minutes) mixed with 0.29 ml (0.44 mmol) of DIBAH (1.5M toluene) at -95°C. It is allowed to come to -85°C within 45 minutes, mixed with 0.15 ml of

NH_4Cl solution and 10 ml of ether while being stirred vigorously, and it is allowed to thaw quickly. After sufficient $MgSO_4$ is added, it is allowed to stir for 1-2 hours and filtered off. After the solvent is removed in Rotavapor, the crude aldehyde is purified by column chromatography (Hx/EE = 3:1), and 140 mg (85%) of aldehyde 11a is obtained as a colorless oil.

IR (Film): ν_{max} 2930, 2781, 1727, 1677, 1076, 919, 836.





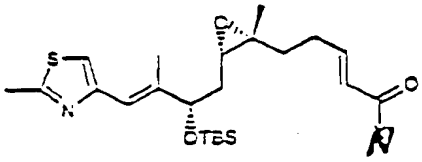
$C_{33}H_{52}N_2O_5S_2Si$
Mol. Wt.: 648,99

4 ml of absolute ether at 0°C and 0.32 ml of nBuLi (1.6M, hexane, 0.51 mmol) are introduced under Ar atmosphere and mixed with 0.36 ml of THF/H_2O (19:1, 1 mmol of H_2O). After 5 minutes, 193 mg of phosphonate (0.49 mmol, dissolved in 1 ml of THF) is added in drops, and after another 10 minutes, 135 mg (0.33 mmol, dissolved in 1 ml of THF) of aldehyde 11a is added in drops. The cooling bath is removed, and after 30 minutes at room temperature, it is quenched with 4 ml of saturated NH_4Cl solution, the phases are separated, and the aqueous phase is extracted with ether (2x 5 ml). The combined organic phases are dried ($MgSO_4$), and the solvent is removed in Rotavapor.

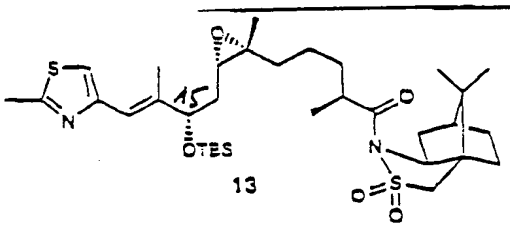
Preparative column chromatography (Hx/EE = 3:1) yields 194 mg (91%) of enoylsultam 12 as a viscous oil, which solidifies like a foam after freezing-out.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (dt, J = 14.8, 7.3 Hz, 1H), 6.91 (s, 1H), 6.55 (d, J = 14.8 Hz, 1H), 6.49 (s, 1H), 4.32 (dd, J = 8.8, 3.8 Hz, 1H), 3.90 (dd, J = 7.3, 5.3 Hz, 1H), 3.48 (d, J = 13.8 Hz, 1H); 3.40 (d, J = 13, 8 Hz, 1H), 2.89 (dd, J = 7.5, 4.5 Hz, 1H), 2.68 (s, 3H), 2.42-2.33 (m, 2H), 2.13-2.02 (m, 2H), 1.99 (s, 3H), 1.95-1.81 (m, 5H), 1.71-1.51 (m, 4H), 1.27 (s, 3H), 1.14 (s, 3H), 0.95 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 164.8, 164.3, 153.4, 149.9, 142.4, 121.6, 119.3, 115.8, 76.8, 65.5, 62.6, 60.7, 53.5, 50.7, 48.8, 48.2, 45.1, 38.9, 36.2, 33.3, 31.9, 28.8, 26.9, 26.2, 22.6, 21.2, 20.3, 19.6, 18.6, 14.4, -4.2, -4.7.

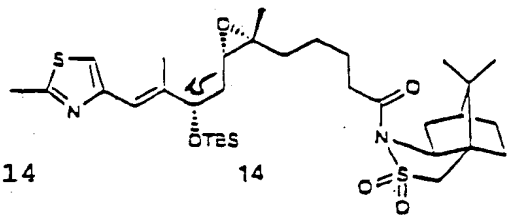


12



13

$C_{34}H_{56}N_2O_5S_2Si$
Mol. Wt.: 666,04



14

$C_{33}H_{54}N_2O_5S_2Si$
Mol. Wt.: 651,01

Conversion at Stage 13 or 14 of OTBS to OTES

172 mg (0.265 mmol) of sultam 12 is dissolved in 5 ml of absolute THF and mixed at -95°C with 0.32 ml of L-selectrides (1.0 M, THF, 0.32 mmol) and heated within 45 minutes to -40°C. After another 15 minutes, it is cooled to -78°C, and after 0.12 ml of HMPA is added, it is mixed with 0.132 ml of MeI. Then, it is heated within 3 hours to 0°C, and after another 2 hours at 0°C, it is quenched by adding 5 ml of NH_4Cl and 10 ml of ether. The phases are separated, and the aqueous phase is extracted with ether (2x 5 ml). The combined organic phases are dried ($MgSO_4$), and the solvent is removed in Rotavapor. Preparative column chromatography (Hx/EE = 3:1) yields 90 mg of **13** and 85 mg of **14**.

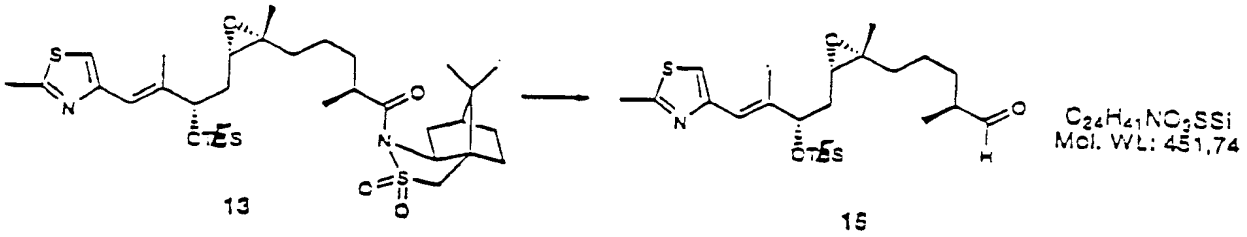
Compound 13

^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.47 (s, 1H), 4.29 (dd, J = 9.0, 3.5 Hz, 1H), 3.85 (t, J = 6.3 Hz, 1H), 3.44 (d, J = 13.5 Hz, 1H), 3.37 (d, J = 3.5 Hz, 1H), 3.07-3.97 (m, 1H), 2.83 (dd, J = 8.0, 4.0 Hz, 1H), 2.66 (s, 3H), 2.02-1.98 (m, 2H), 1.98 (d, J = 1.0 Hz, 3H), 1.92-1.68 (m, 5H), 1.57-1.26 (m, 8H), 1.22 (s, 3H), 1.16 (d, J = 7.0 Hz, 3H), 1.11 (s, 3H), 0.92 (s, 3H), 0.86 (s, 9H), 0.05 (s, 3H), -0.01 (s, 3H).

Compound 14

^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.49 (s, 1H), 4.31 (dd, J = 9.0, 3.5 Hz, 1H), 3.83, (dd, J = 7.3, 5.3 Hz, 1H), 3.45 (d, J = 13.6 Hz, 1H), 3.39 (d, J = 13.6 Hz, 1H), 2.86 (dd, J = 7.8, 4.3 Hz, 1H), 2.75-2.63 (m, 2H), 2.68 (s, 3H), 2.12-2.03 (m, 2H), 2.00 (d, J = 1.0 Hz, 3H), 1.93-1.80 (m, 4H), 1.72-1.30 (m,

9H), 1.24 (s, 3H), 1.12 (s, 3H), 0.93 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H).

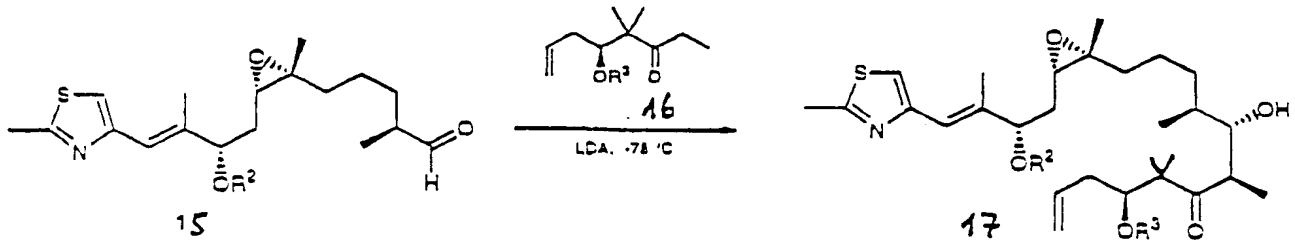


50 mg (0.075 mmol) of sultam 13 is dissolved under argon in 2.5 ml of absolute methylene chloride and mixed slowly with 0.083 ml (0.083 mmol) of DIBAH (1.0 M, toluene) at -95°C. It is allowed to come to -75°C within 2-2.5 hours while being stirred vigorously with 0.05 ml of MeOH and 0.1 ml of NH_4Cl solution, as well as 5 ml of ether, and it is allowed to thaw quickly. After sufficient $MgSO_4$ is added, it is allowed to stir for about 1 hour (even overnight) and filtered off. After the solvent is removed in Rotavapor, the crude aldehyde is purified by column chromatography (Hx/EE = 3:1), and 24 mg (71%) of aldehyde 15 is obtained as a waxy solid.

^1H NMR (400 MHz, $CDCl_3$) δ 9.58 (d, J = 5.0 Hz, 1H), 6.90 (s, 1H), 6.49 (s, 1H), 4.31 (dd, J = 9.0, 4.0 Hz, 1H), 2.87 (dd, J = 7.0, 4.5 Hz, 1H), 2.68 (s, 3H), 2.36-2.26 (m, 1H), 2.00 (s, 3H), 1.92-1.84 (m, 1H), 1.74-1.64 (m, 1H), 1.60-1.52 (m, 1H), 1.50-1.32 (m, 5H), 1.26 (s, 3H), 1.08 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100.6 MHz $CDCl_3$) δ 205.2, 164.9, 153.4, 142.5, 119.2, 115.8, 76.7, 62.4, 61.1, 46.7, 36.4, 33.6, 31.0, 26.2, 23.3, 22.7, 19.6, 18.6, 14.4, 13.7, -4.2, -4.7.

Aldol Reaction



15 17

Example: R^2 = TES, R^3 = TBS

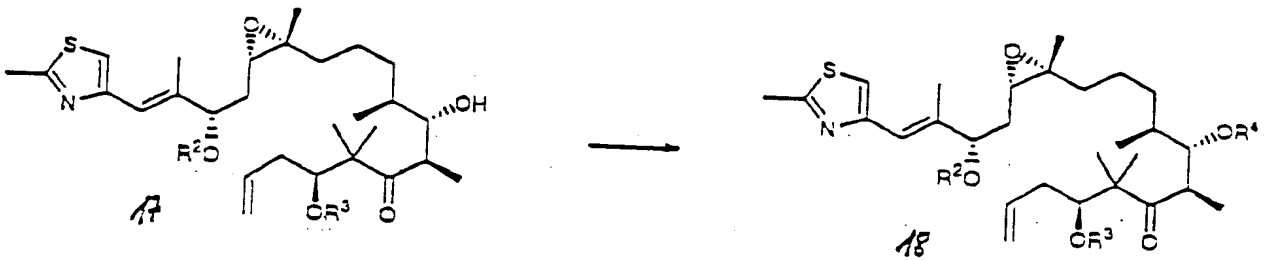
1.75 ml (1.23 mmol) of isopropylamine is dissolved in 4 ml of absolute THF and mixed at -45°C with 0.75 ml of nBuLi (1.6 M in hexane; 1.20 mmol), heated to 0°C after 5 minutes and stirred for 20 minutes at 0°C. After cooling to -78°C, 345 mg (1.21 mmol) of ketone 16 (dissolved in 1 ml of THF) is added in drops within 2 minutes, and the reaction mixture is heated to -40°C within 30 minutes. It is again cooled to -78°C, and 532 mg (1.18 mmol) of aldehyde 15 (dissolved in 1.5 ml of THF) is added in drops within 2-3 minutes. After 15 minutes at -78°C, it is quenched with 4 ml of saturated NH_4Cl solution while being stirred vigorously (initially slowly then quickly added), 6 ml of ether is added, and the cooling bath is replaced by a water bath. After thawing, some water is added, and the phases are separated after shaking out. Extraction with ether, drying ($MgSO_4$),

removal of the solvent and subsequent column chromatography (hexane/ethyl acetate 10:1 → 5:1) yield 668 mg (77%) of desired main isomer 17 as a colorless, viscous liquid.

Compound 17 (R^2 = TES, R^3 = TBS)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.93 (s, 1H), 6.51 (s, 1H), 5.72 (ddt, J = 17.1, 10.0, 7.0 Hz, 1H), 4.99 (m, 2H), 4.33 (dd, J = 9.0, 3.5 Hz, 1H), 3.92 (d, J = 6.3, 4.3 Hz, 1H), 3.49 (s, 1H), 3.31 (d, J = 9.0 Hz, 1H), 3.25 (q, J = 7.0 Hz, 1H), 2.88 (dd, J = 7.5, 4.0 Hz, 1H), 2.70 (s, 3H), 2.24-2.06 (m, 2H), 2.01 (d, J = 1.0 Hz, 3H), 1.95-1.87 (m, 1H), 1.82-1.72 (m, 1H), 1.63-1.45 (m, 5H), 1.41-1.30 (m, 1H), 1.28 (s, 3H), 1.18 (s, 3H), 1.20-1.05 (m, 1H), 1.12 (s, 3H), 1.03 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.83 (d, J = 7.0 Hz, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 222.5, 164.4, 153.1, 142.2, 136.3, 118.8, 116.7, 115.3, 76.5, 76.4, 74.9, 62.1, 61.1, 54.3, 41.1, 39.6, 36.0, 35.6, 33.4, 33.1, 26.05, 25.9, 23.4, 22.7, 22.4, 19.4, 19.2, 18.24, 18.21, 15.3, 14.0, 9.7, -3.5, -4.90, -4.6, -5.1.

7-OH Protection



Example: R^2 = TES, R^3 = TBS, R^4 = Troc

200 mg (0.27 mmol) of aldol 17 is dissolved in 10 ml of methylene chloride and 5 ml of pyridine and mixed at 20°C (water bath) with 0.5 ml (2.4 mmol) of chloroformic acid-2,2,2-trichloroethyl ester and stirred for 30-45 minutes at room temperature. For working-up, the reaction mixture is shaken out with 50 ml of saturated $NaHCO_3$ solution and 40 ml of methylene chloride. Extraction with methylene chloride, drying ($MgSO_4$), removal of the solvent and subsequent column chromatography (hexane/ethyl acetate 10:1) yield 231 mg (94%) of desired product 18 as a colorless oil.

Compound 18 (R^2 = TES, R^3 = TBS, R^4 = Troc)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.92 (s, 1H), 6.51 (s, 1H), 5.79 (ddt, J = 16.6, 10.5, 7.0 Hz, 1H), 5.05-4.97 (m, 2H), 4.85 (d, J = 12.1 Hz, 1H), 4.81 (dd, J = 7.0, 4.5 Hz, 1H), 4.69 (d, J = 12.1 Hz, 1H), 4.33 (dd, J = 9.0, 3.5 Hz, 1H), 3.75 (dd, J = 6.5, 4.0 Hz, 1H), 3.44 (m, 1H), 2.88 (dd, J = 7.5, 4.0 Hz, 1H), 2.70 (s, 3H), 2.28-2.19 (m, 1H), 2.06-1.95 (m, 1H), 2.02 (s, 3H), 1.92-1.84 (m, 1H), 1.75-1.65 (m, 1H), 1.57-1.41 (m, 5H), 1.33-1.11 (m, 2H), 1.30 (s, 3H), 1.27 (s, 3H), 1.21-1.12 (m, 1H), 1.07 (d, J = 7.0 Hz, 3H), 1.04 (s, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 215.6, 164.4, 154.2, 153.1, 142.1, 136.4, 118.9, 116.6, 115.4, 94.8, 82.9, 78.1, 76.6, 76.4, 62.1, 60.8, 54.0, 42.3, 39.4, 36.0, 35.0, 33.3, 31.8, 26.1, 25.9, 24.0, 22.7, 22.3, 20.0, 19.2, 18.23, 18.21,

16.1, 14.0, 11.5, -3.6, -3.9, -4.6, -5.1. **IR** (film) $\hat{\upsilon}_{max}$ = 2956, 2930, 2858, 1760, 1699, 1472, 1384, 1251, 1081, 992, 928, 836, 777, 732. **Rotation:** $[\alpha]^{20}_{D}$ = -30 (c = 1.4, CH_2Cl_2). **Analysis** Cld. for $C_{43}H_{74}Cl_3NO_7SSi_2$ (911,65): C 56.65, H 8.18, N 1.54, Fnd.: C 56.54 H 8.18 N 1.47.

Dihydroxylation/Glycol Cleavage

Example: R^2 = TES, R^3 = TBS, R^4 = Troc

148 mg (0.162 mmol) of alkene 18 is dissolved in 8 ml of THF-tBuOH (1:1) and mixed with 2 mg of OsO4 (5 mol%) and 0.89 ml of NMO (0.2 M in H_2O, 0.178 mmol). After 16 hours of stirring at 25°C, it is shaken out vigorously and for a long time with 10 ml of $Na_2S_2O_3$ (10% in H_2O) and 15 ml of methylene chloride. The phases are separated, and the aqueous phase is extracted three more times with methylene chloride. Drying ($MgSO_4$), removal of the solvent and filtration via a short silica gel column (hexane/ethyl acetate 1:1) yields 131 mg (86%) of diol as an isomer mixture, which is further used without additional purification.

131 mg (0.139 mmol) of diol is dissolved in 15 ml of ethanol and 3 ml of H_2O and mixed with 90 mg (0.420 mmol) of $NaIO_4$.

After three hours of stirring at 25°C, it is shaken out with 30 ml of semi-saturated $NaHCO_3$ solution and 30 ml of ether, and the phases are separated. Extraction with ether, drying ($MgSO_4$), removal of the solvent and subsequent column chromatography (Hexane/ethyl acetate 10:1 → 5:1) yield 115 mg (78% in terms of alkene) of aldehyde 19 as a colorless oil.

Compound 19 (R^2 = TES, $R^{3'}$ = TBS, R^4 = Troc)

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 9.73 (dd, J = 2.0, 1.0 Hz, 1H), 6.92 (s, 1H), 6.50 (s, 1H), 4.83 (d, J = 12.0 Hz, 1H), 4.74 (dd, J = 7.5, 4.0 Hz, 1H), 4.67 (d, J = 11.8 Hz, 1H), 4.36-4.29 (m, 2H), 3.49-3.38 (m, 1H), 2.88 (dd, J = 7.5, 4.0 Hz, 1H), 2.70 (s, 3H), 2.67 (ddd, J = 17.5, 4.5, 1.0 Hz, 1H), 2.39 (ddd, J = 17.5, 5.5, 2.0 Hz, 1H), 2.39 (s, 3H), 1.88 (ddd, J = 13.9, 9.4, 4.0 Hz, 1H), 1.76-1.66 (m, 1H), 1.60-1.40 (m, 5H), 1.35-1.10, (m, 2H), 1.33 (s, 3H), 1.26 (s, 3H), 1.20 (d, J = 6.5 Hz, 1H), 1.02 (s, 3H), 0.97 (d, J = 6.5 Hz, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), ^{13}**C NMR** (100.6 MHz, $CDCl_3$): δ = 215.4, 200.2, 164.2, 154.2, 153.0, 142.1, 118.9, 115.4, 94.7, 82.3, 76.65, 76.3, 72.3, 62.1, 60.8, 53.4, 49.3, 42.2, 35.9, 34.9, 3.33, 31.9, 25.87, 25.85, 23.0, 22.6, 22.3, 20.0, 19.2, 18.2, 18.1, 15.9, 14.0, 11.1, -4.4, -4.5, -4.6, -5.1. **IR** (Film) $\dot{\upsilon}_{max}$ = 2956, 2930, 2885, 2857, 1759, 1726, 1699, 1472, 1384, 1361, 1252, 1082, 992, 927, 836, 777, 734. **Rotation:** $[\alpha]^{20}_D$ = -42.7 (c = 1.2, $CHCl_3$)

15-O-Protection Removal

Example: R_2 = TES, R^3 = TBS, R^4 = Troc

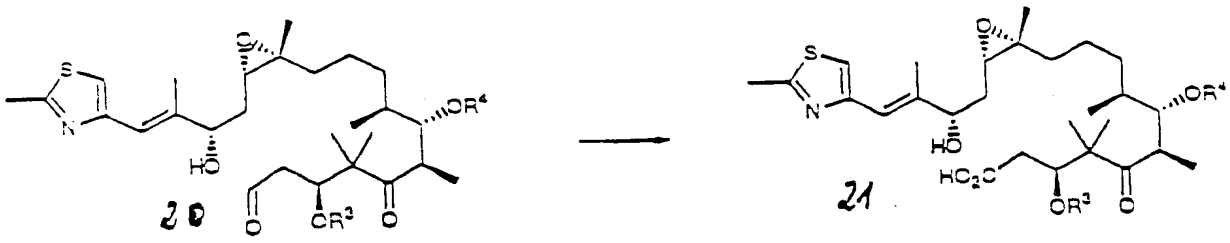
68 mg (0.074 mmol) of 19 is dissolved in a polypropylene reaction vessel (with a cover) in 2.5 ml of absolute THF and mixed with 2.5 ml of a standard solution of HF-pyridine (produced from: 5 ml of HF-pyridine, 15 ml of pyridine and 10 ml of THF) that is buffered with pyridine. After 30 minutes, the reaction is completed. For working-up, 80 ml of saturated $NaHCO_3$ solution is introduced, and the reaction mixture is carefully added (plastic syringe) while being stirred vigorously. After extraction with ether (4 times 25 ml) and drying ($MgSO_4$), the solvent is removed in Rotavapor, whereby the pyridine is removed by repeated spinning-in with toluene. The residue is put on a column with deactivated silica gel (hexane/ethyl acetate 2:1 → 1:1), and 51 mg (92%) of product 20 is obtained as a pale yellow, viscous oil.

Compound 20 (R^3 = TBS, R^4 = Troc)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.74 (s, 1H), 6.95 (s, 1H), 6.60 (s, 1H), 4.84 (d, J = 12.0 Hz, 1H), 4.75 (dd, J = 7.8, 4.3 Hz, 1H), 4.68 (d, J = 12.0 Hz, 1H), 4.41-4.35 (m, 1H), 4.34 (t, J

= 4.8 Hz, 1H); 3.49-3.41 (m, 1H), 2.96 (dd, J = 8.0, 4.0 Hz, 1H), 2.96 (s, 3H), 2.67 (dd, J = 17.5 Hz, 4.0 Hz, 1H), 2.40 (ddd, J = 17.5, 5.5, 2.0 Hz, 1H), 2.09 (d, J = 3.5 Hz, 1H), 2.06 (s, 3H), 1.94 (ddd, J = 14.6, 8.5, 4.0 Hz, 1H), 1.78-1.68 (m, 1H), 1.67 (ddd, J = 14.0, 8.0, 4.0 Hz, 1H), 1.58-1.41 (m, 4H), 1.35-1.25 (m, 1H), 1.34 (s, 3H), 1.28 (s, 3H), 1.07 (d, J = 6.5 Hz, 3H), 1.04 (s, 3H), 0.98 (d, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.11 (s, 3H), 0.03 (s, 3H), **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 215.4, 200.5, 164.6, 154.2, 152.7, 141.7, 118.9, 94.7, 82.3, 76.7, 75.4, 72.2, 61.8, 60.7, 53.4, 49.3, 42.2, 34.9, 34.1, 33.2, 32.0, 25.9, 23.0, 22.6, 22.1, 20.0, 19.2, 18.1, 15.9, 14.5, 11.2, -4.4, -4.5.

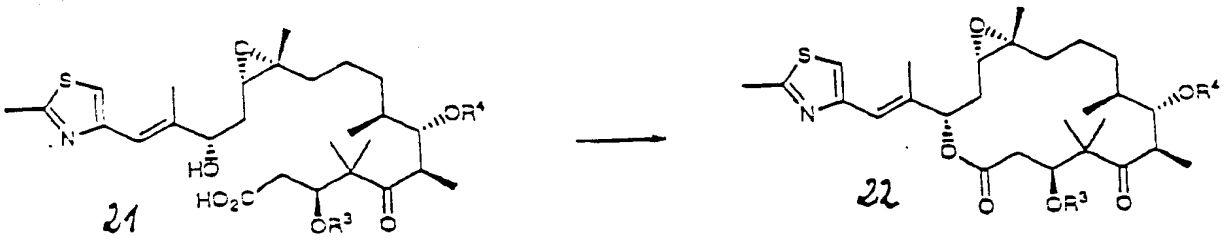
Pinnick-Oxidation/Macrolactonization



Example: R^3 = TBS, R^4 = Troc

54 mg (0.068 mmol) of aldehyde 20 is dissolved in 2.5 ml of tBuOH and 2.5 ml of 2,3-dimethyl-2-butene and mixed with a solution of 30 mg of $NaClO_2$ and 30 mg of NaH_2PO_4 in 0.5 ml of H_2O and stirred for 45 minutes at room temperature. For working-up, the reaction mixture is mixed with 20 ml of semi-saturated NH_4Cl solution and extracted with methylene chloride (4 x 10 ml).

After drying, the solvent is removed, and crude acid 21 (51 mg) that is thus obtained is used directly in the next reaction.



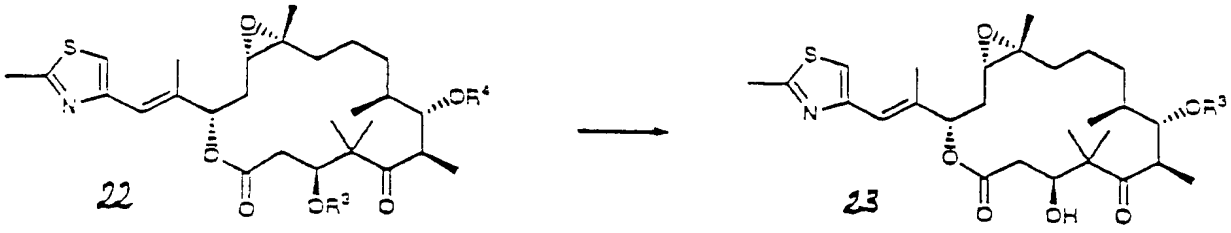
51 mg (0.062 mmol) of crude acid 21 is dissolved in 1.5 ml of absolute THF and mixed at 0°C with 57 µl (0.36 mmol) of triethylamine and 43 µl (0.24 mmol) of 2,4,6-trichlorobenzoyl chloride and stirred for 20 minutes at room temperature. The active ester that is thus produced is slowly added in drops (15 minutes) to a solution of 80 mg (0.60 mmol) of DMAP in 35 ml of absolute toluene and stirred for 2 hours at room temperature (25°C). The reaction mixture is concentrated by evaporation to about 5 ml and filtered on a short silica gel column (rewashed with 30 ml of hexane/ethyl acetate). Removal of the solvent and subsequent column chromatography (hexane/ethyl acetate 4:1) yield 18 mg (34%) of macrolactone 22 as a colorless oil.

Compound 22 (R^3 = TBS, R^4 = Troc)

^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.99 (s, 1H), 6.56 (s, 1H), 5.21-5.14 (m, 2H), 4.87 (d, J = 12.0 Hz, 1H), 4.75 (d, J = 12 Hz, 1H), 4.05 (d, J = 9.8 Hz, 1H), 3.30 (dq, J = 10.2, 6.3 Hz, 1H), 2.82 (dd, J = 10.3, 4.0 Hz, 1H), 2.79 (dd, J = 16.5, 1.5 Hz, 1H),

2.71 (s, 3H), 2.64 (dd, J = 16.5, 10.0 Hz, 1H), 2.25-2.21 (m, 1H), 2.11 (s, 3H), 1.93-1.64 (m, 4H), 1.55-1.42 (m, 2H), 1.32-1.24 (m, 1H), 1.28 (s, 3H), 1.21 (s, 3H), 1.19 (s, 3H), 1.16-1.08 (m, 1H), 1.12 (d, J = 6.7 Hz, 3H), 1.03 (d, J = 6.7 Hz, 3H), 0.88 (s, 9H), 0.16 (s, 3H), -0.03 (s, 3H).

Protection Removal at 3-O



Example: R^3 = TBS, R^4 = Troc

18 mg (23 μmol) of macrolactone 22 is dissolved in 0.5 ml of THF and mixed with 2.5 ml of buffered HF-Py (see above) and stirred for 72 hours at room temperature, and then it is added carefully to 35 ml of a saturated $NAHCO_3$ solution and extracted with ether. Removal of the solvent (repeated spinning-in with toluene) and subsequent column chromatography (hexane/ethyl acetate 2:1 → 1:1) yield 5 mg (32%) of desired product 23 as a colorless oil. At the same time, 6 mg of starting material is recovered.

Compound 23 (R^4 = Troc)

^1H NMR (250 MHz, $CDCl_3$): δ = 6.99 (s, 1H), 6.63 (s, 1H), 5.52 (t, J = 4.5 Hz, 1H), 5.18 (dd, J = 9.0, 2.0 Hz, 1H), 4.84 (d, J = 12 Hz, 1H), 4.78 (d, J = 12 Hz, 1H), 4.15-4.05 (m, 1H), 3.79-3.70 (m, 2H), 3.64-3.52 (m, 1H), 2.87 (t, J = 6.0 Hz, 1H), 2.72 (s, 3H), 2.59 (dd, J = 14.0, 10.0 Hz, 1H), 2.48 (dd, J = 14.0, 4.0 Hz, 1H), 2.35 (t, J = 7.5 Hz, 2H), 2.12 (s, 3H), 2.00 (t, J = 5.5 Hz, 2H), 1.89-1.81 (m, 2H), 1.75-1.25 (m, 3H), 1.39 (s, 3H), 1.28 (s, 3H), 1.15 (d, J = 7.0 Hz, 3H), 1.09 (s, 3H), 0.99 (d, J = 7.0 Hz, 3H).

7-O-Protection Removal → Epothilone B

Example: R^4 = Troc

2.7 mg (4.4 µmol) of 23 is dissolved in 1.5 ml of ethanol, mixed with 25 mg of NH_4Cl and 25 mg of zinc (powder) and refluxed for 30 minutes. After cooling to room temperature, it is filtered on Celite, washed with ethyl acetate, and the solvent is removed in Rotavapor. Subsequent column chromatography (hexane/ethyl acetate 1:1) yields 1.4 mg (about 90%) of 24 (epothilone B).

Compound 24 (Epothilone B)

^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.97 (s, 1H), 6.60 (s, 1H), 5.41 (d, J = 7.8, 2.4 Hz, 1H), 4.27-4.18 (m, 2H), 3.77 (s, 1H), 3.30 (m, 1H), 2.81 (dd, J = 7.5, 4.5 Hz, 1H), 2.70 (s, 3H), 2.65 (sbr, 1H), 2.54 (dd, J = 14.0, 10.2 Hz, 1H), 2.37 (dd, J = 14.0, 3.0 Hz, 1H), 2.13-2.05 (m, 1H), 2.09 (s, 3H), 1.92 (ddd, J = 15.3, 7.7, 7.7 Hz, 1H), 1.78-1.68 (m, 2H), 1.55-1.46 (m, 2H), 1.45-1.33 (m, 2H), 1.37 (s, 3H), 1.30-1.22 (m, 1H), 1.28 (s, 3H), 1.25 (s, 3H), 1.17 (d, J = 6.7 Hz, 3H), 1.08 (s, 3H), 1.01 (d, J = 7.0 Hz, 3H).

NMR data are identical to the data of K. C. Nicolaou and A. Mantoulidis (Tet. Lett. 39 (1998) 8633-8636). HPLC analysis with a comparison sample of A. Mantoulidis shows identical material.

Preparative Methods:

All reactions of organometallic reagents and all reactions in absolute solvents are performed in an air-free and moisture-free environment. The glass equipment that is used is heated several times in a vacuum (about 0.01 mbar) before the beginning of the test and aerated with dry argon of the Linde Company. Unless otherwise indicated, all reaction batches are stirred magnetically.

Methylene chloride is predried on a basic aluminum oxide column of activity stage I (Woelm) and made absolute on calcium hydride. After predrying on a basic aluminum oxide column over an 8:1 sodium/potassium alloy, diethyl ether is refluxed until stable blue coloring of the benzophenone indicator is achieved, and it is freshly distilled off before use. The tetrahydrofuran (THF) is predried over KOH, filtered on a column that is coated with basic aluminum oxide and then distilled on potassium with triphenylmethane as an indicator.

After predrying over calcium chloride just like hexane (Hex) before use for column chromatography in a rotary evaporator, the ethyl acetate (EE) is distilled off.

Chromatographic Process:

All reactions are monitored by thin-layer chromatography (TLC) on silica gel-60-aluminum foils with UV-indicator F_{254} of the Merck Company. As a mobile solvent, in most cases solvent mixtures that consist of hexane (Hex) and ethyl acetate (EE) are used. For visualization of non-UV-active substances, in most

cases anisaldehyde/glacial acetic acid/sulfuric acid (1:100:1) has been taken as a standard dip reagent.

The preparative column chromatography is performed on silica gel-60 of the Merck Company (0.04-0.063 mm, 230-400 mesh), whereby solvent mixtures that consist of hexane (Hex) and ethyl acetate (EE) or diisopropyl ether are used as eluants.

On an analytical scale as well as on a preparative scale, the high-pressure liquid chromatographic separations (HPLC) are performed on modular systems of the Knauer Company (pump 64, UV and RI detectors, columns and recorders), Waters/Millipore Company (injection system U6K9) and Milton-Roy (integrator CI-10). For the analytical HPLC, in most cases a Knauer column (4·250 mm) with 5 μm of nucleosil is used, and for the preparative HPLC, a column (16·250 mm, 32·250 mm or 64·300 mm) with 7 μm or 5 μm nucelosil 50 is used.

Dye Reagents

Dye Reagent I (F I): In the case of most compounds that can be reduced, 1 g of cerium(IV) sulfate in 10 ml of concentrated sulfuric acid and 90 ml of water yield an intensive blue color reaction during drying.

Dye reagent II (F II): A 10% ethanolic solution of molbydatophosphoric acid represents another dip reagent for detecting unsaturated and reducible compounds. In contrast to dye reagent I, the molybdate dye reagents, especially pertaining to several functionalities, shows a broader color spectrum in the case of virtually identical reliability.

Dye reagent III (F III): 1 ml of anisaldehyde in 100 ml of ethanol and 2 ml of concentrated sulfuric acid represents an extremely sensitive dye reagent that in addition also shows probably the broadest color spectrum.

Dye reagent IV (F IV): Like the anisaldehyde reagent, 1 g of vanillin in 100 ml ethanol and 2 ml of concentrated sulfuric acid is a very sensitive dye reagent with a broad color spectrum.

Dye reagent V (F V): 1 g of 2,4-dinitrophenylhydrazine in 25 ml of ethanol, 8 ml of water and 5 ml of concentrated sulfuric acid represent an excellent dip reagent that responds selectively to aldehydes even without being heated and that responds somewhat more slowly to ketones.

Dye reagent VI (F VI): A 0.5% aqueous solution of potassium permanganate indicates groups that can be oxidized by decolorization, whereby unsaturated, non-aromatic structural units react spontaneously without heating.

Spectroscopic Process and General Analysis:

NMR-Spectroscopy

The ^{1}H-NMR spectra are recorded as an internal standard with a DRX 250 DRX 400 spectrometer of the Bruker Company with the substances as a solution in deuterated solvents and tetramethylsilane. The evaluation of the spectra is carried out according to rules of the first order. If a signal multiplicity that occurs cannot be explained in this way, the indication of the observed line set is done. To determine the stereochemistry, the NOE-spectroscopy (Nuclear Overhauser Effect) is used.

To characterize the signals, the following abbreviations are used: s (singlet), d (doublet), dd (double doublet), ddd (6-line system with two identical coupling constants or an 8-line system in three different coupling constants), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), m (multiplet), mc (centered multiplet), br (broad), hv (semi-masked signal) and v (masked signal).

The ^{13}C NMR spectra are measured as an internal standard with an AC 250 of the Bruker Company with a $CDCl_3$ signal at 77.0 ppm, whereby the proton resonances are wideband-coupled.

IR-Spectroscopy

The infrared spectra are recorded with devices of the Perkin-Elmer Company (model 257 or 580 B) and Nicolet Company (FTIR-interferometer system 55XC). The oils are measured as films between potassium bromide disks. The bands are indicated according to decreasing wave number (cm^{-1}). For characterization, the following designations are selected: vs (very strong), s (strong), m (medium), w (weak).

Abbreviations:

abs.: absolute, **Ar:** aryl/aromatic compound, **Cld.:** calculated, **Brine:** cold, saturated common salt solution, **nBuLi:** nbutyllithium, **c:** concentration, **COSY:** correlated spectroscopy (correlated spectroscopy), **CSA:** camphersulfonic acid, **TLC:** thin-layer chromatography, **DCM:** dichloromethane, **DDQ:** dichloro-dicyano-quinone, **d.e.:** diastereomeric excess, **DIBAH:** diisobutyl-

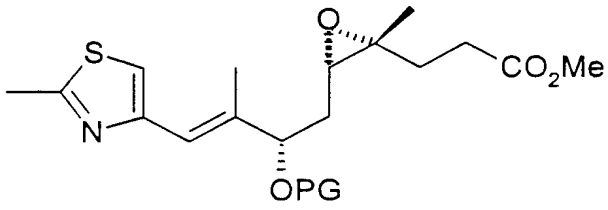
aluminum hydride, **DIPA:** diisopropylamine, **DMAP:** dimethylaminopyridine, **DMF:** N,N'-dimethylformamide, **DMS:** dimethyl sulfide, **DMSO:** dimethyl sulfoxide, **ds:** diastereoselection, **EA:** elementary analysis, **e.e.:** enantiomeric excess, **EE:** ethyl acetate, **EI:** electron impact ionization, **eq:** equivalent(s), **eV:** electron volt, **FG:** functional group, **FI:** field ionization, **gef.:** found, **ges.:** saturated, **h:** hour(s), **Hex:** n-hexane, **HMDS:** hexamethyldisilazide, **HPLC:** high-pressure liquid chromatography, **Hünig Base:** N-ethyl-diisopropylamine, **HRMS:** high resolution mass spectrometry, **HV:** high vacuum, **iPrOH:** 2-propanol, **IR:** infrared spectrometry/infrared spectrum, **J:** coupling constant, **LDA:** lithium diisopropylamine, **Lsg.:** solution, **Lsm.:** solvent, **MC:** methylene chloride, **Me:** methyl, **MeLi:** methyllithium, **min.:** minute(s), **MS:** mass spectrometry/mass spectra, **NMR:** nuclear magnetic resonance, **NOE:** Nuclear Overhauser Effect, **PCC:** pyridinium chlorochromate, **PG:** protective group, **Ph:** phenyl, **ppm:** parts per million, **Rkt.:** reaction, **rt.:** retention time, **RT:** room temperature (20-30°C), **Std.:** hour(s), **TBAF:** tetra-n-butylammonium fluoride, **TBDPS:** tert-butyldiphenyl-silyl chloride, **TBDPSCl:** tert-butyldiphenyl-silyl chloride, **TBS:** tert-butyldimethyl-silyl chloride, **TBSCI:** tert-butyldimethyl-silyl chloride, **TBSTriflate:** tert-butyldimethyl-silyl-triflate, **TEA:** triethylamine, **tert/t:** tertiary, **TFA:** trifluoroethanoic acid, **TFAA:** trifluoroethanoic acid anhydride, **TFMS:** trifluoromethanesulfonic acid, **THF:** tetrahydrofuran, **TMS:** trimethylsilyl-, **u:** $g \cdot mol^{-1}$.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. In a process for the production of epothilone compounds, the improvement comprising preparing said compounds by cyclization of a compound produced from an intermediate of formula II



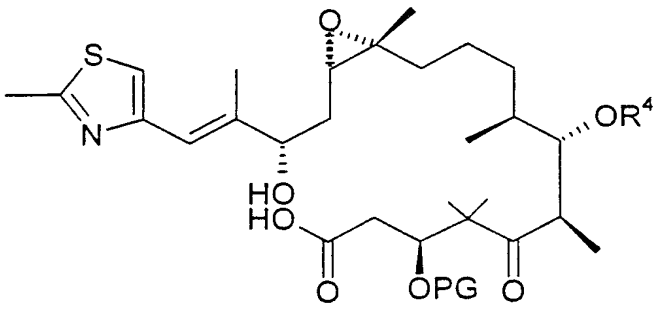
II

wherein PG is a protecting group.

2. The process according to claim 1, wherein PG is a TBS or TES group.

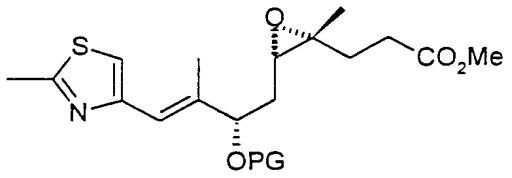
3. The process according to claim 1, wherein the compound of formula II contains a TBS group as PG, which group is changed to a TES group during the process.

4. The process according to claim 1, wherein said cyclization reaction is of a compound of the formula 21



21

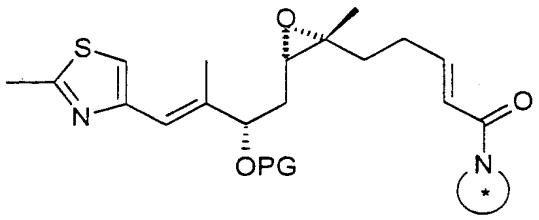
5. The process according to claim 4, wherein the compound of formula 21 is produced by a process comprising reducing a compound of formula 11



11

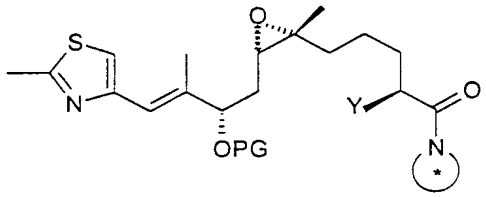
to form an aldehyde, coupling the aldehyde with a compound

to produce an enoylsultam of formula 12,



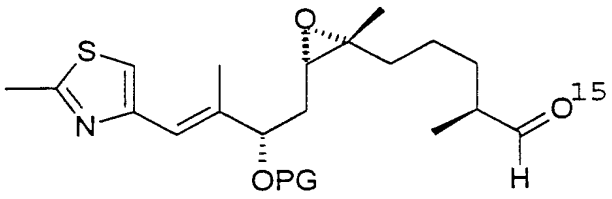
12

reacting enolysultam 12 with L-selectrides to produce compcunds of formulae 13 and 14,



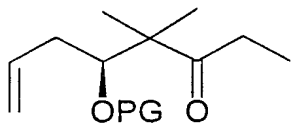
13 (Y=Me)
14 (Y=H)

reducing sultam 13 to form aldehyde 15,



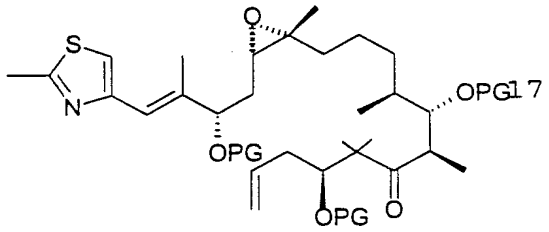
15

reacting 15 with ketone 16

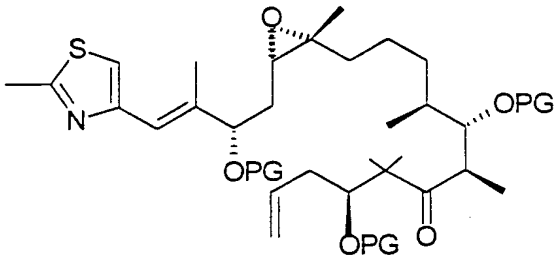


16

to form compound 17,

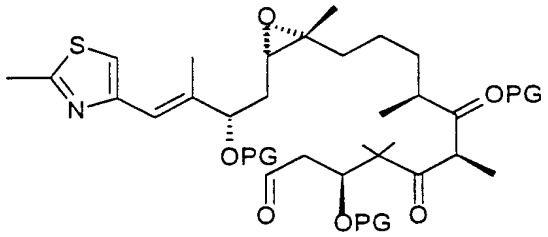


protecting the 17-OH group of compound 17 so as to produce alkene 18,



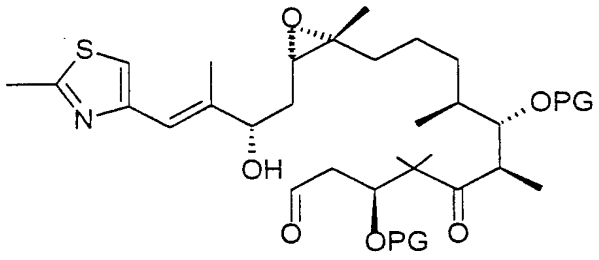
18

subjecting alkene 18 to dehydroxylation and glycocleavage to produce aldehyde 19,



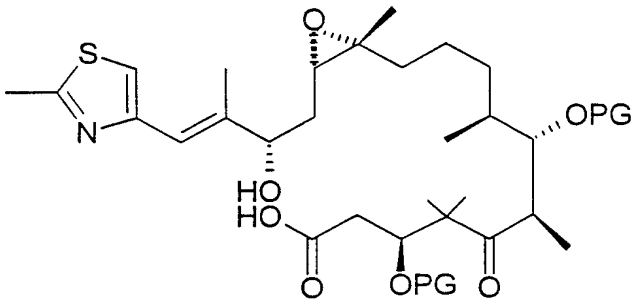
19

deprotecting the 15-position of aldehyde 19 to produce aldehyde 20,



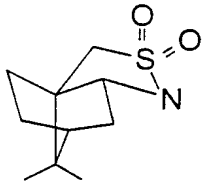
20

and subjecting aldehyde 20 to oxidation and macrolactonization to produce compound 21

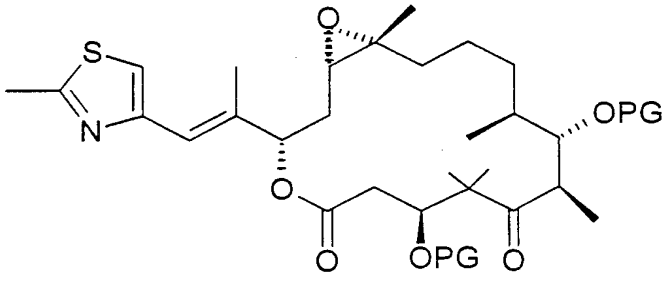


21

wherein each PG independently is a protecting group,

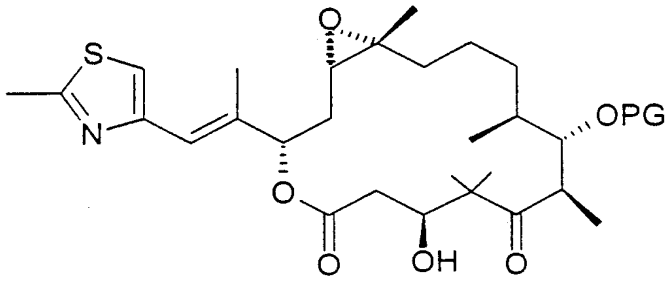
and  is 

6. A process according to claim 4, comprising cyclizing a compound of formula 21 to produce a macrolactone of formula 22



22

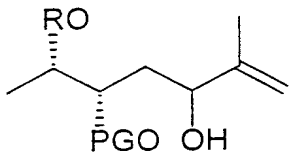
deprotecting the oxygen atom at the 3-position to form a compound of formula 23



23

and removing the protecting group at the 7-position to form epothilone B.

7. A compound of the formula 5 to 21



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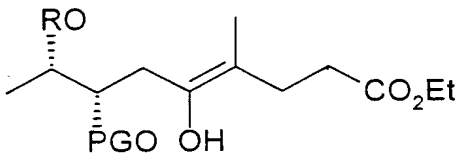

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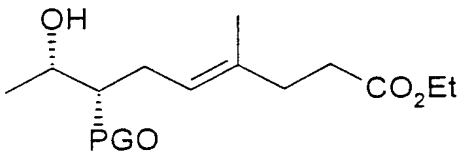

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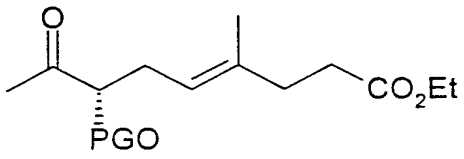

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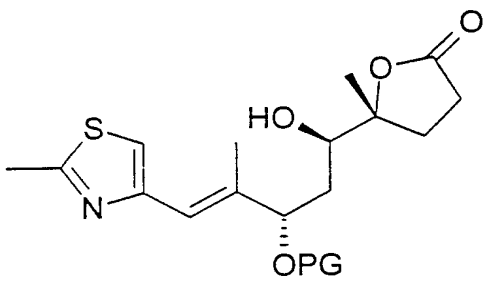

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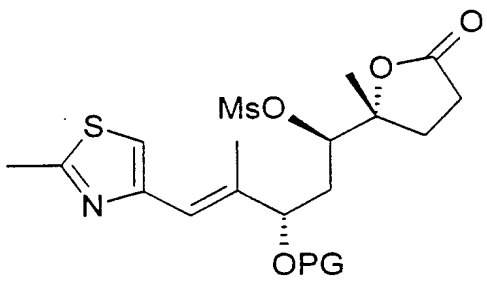

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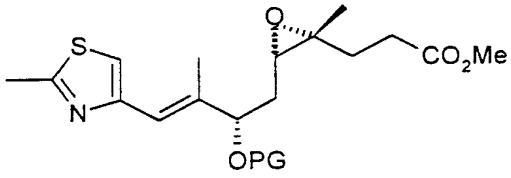

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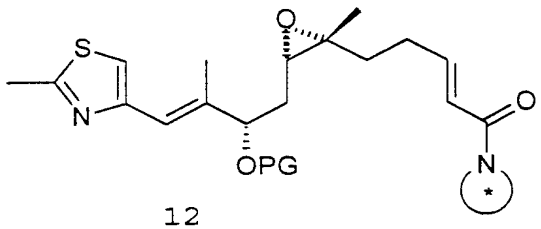

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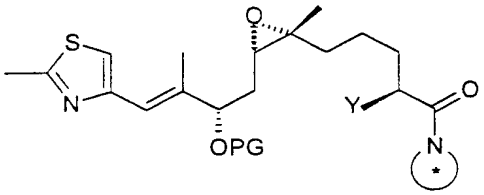
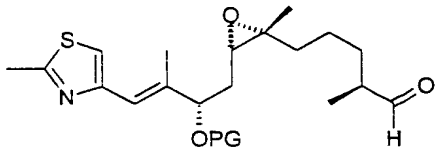


13 (Y=Me)

14 (Y=H)



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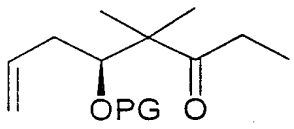

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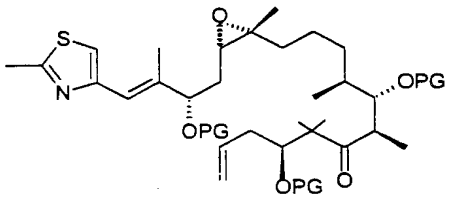

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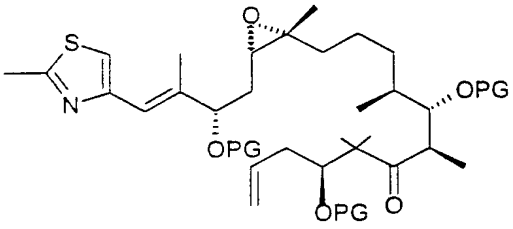

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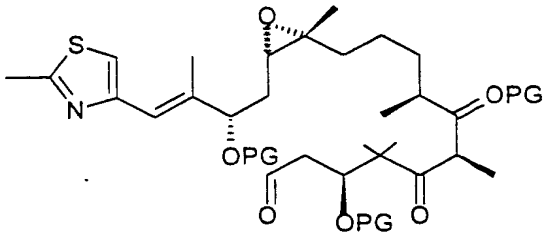

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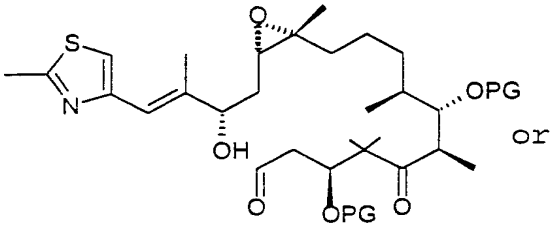
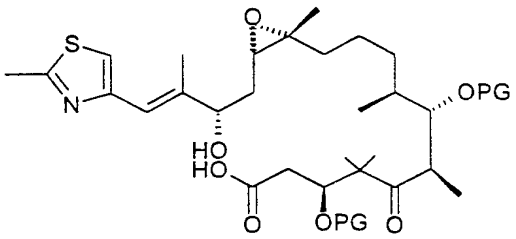


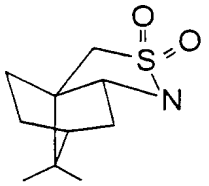
or



20 21

wherein PG is a protecting group,

-N* is



and R is Bn or PMB.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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(43) International Publication Date
1 February 2001 (01.02.2001)

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(10) International Publication Number
WO 01/07439 A3

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(25) Filing Language: English

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US 60/145,005 (CIP)
Filed on 22 July 1999 (22.07.1999)

(71) Applicant *(for all designated States except US)*: **SCHERING AKTIENGESELLSCHAFT** [DE/US]; D-13342 Berlin (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MULZER, Johann** [DE/DE]; Friedridsthaler Weg 20, D-13467 Berlin (DE). **MARTIN, Harry** [DE/AT]; Westbahnstrasse 56/2/8, A-1070 Wien (AT).

(74) Agents: **SHUBIN, Harry, B.** et al.; Millen, White, Zelano & Branigan, P.C., Arlington Courthouse Plaza 1, Suite 1400, 2200 Clarendon Boulevard, Arlington, VA 22201 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

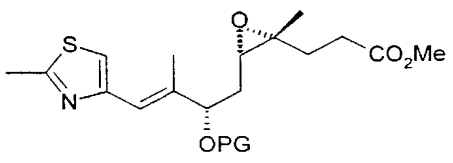
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(88) Date of publication of the international search report:
3 May 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PRODUCTION OF EPOTHIOLONE B AND DERIVATIVES AS WELL AS INTERMEDIATE PRODUCTS FOR THIS PROCESS



(II)

(57) Abstract: The present invention is directed to a process for the production of epothilone compounds, the improvement comprising preparing said compounds by cyclization of a compound produced from an intermediate of formula (II) wherein PG is a protecting group.

WO 01/07439 A3

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 00/20064

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/06 C07D493/04 C07D275/06 C07D417/14 C07F7/18
//(C07D493/04,313:00,303:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NICOLAU K.C. ET AL: "Total syntheses of epothilones A and B via a macro-lactonization-based strategy" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 119, no. 34, 27 August 1997 (1997-08-27), pages 7974-7991, XP002156412 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 cited in the application the whole document	1-6
X	page 7975, scheme 2, compound 19	7
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 January 2001	23/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beslier, L

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 00/20064

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 19086 A (GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FORSCHUNG MBH) 29 May 1997 (1997-05-29) cited in the application the whole document	1-6
X	claim 7	7
P,X	MARTIN H.J. ET AL.: "How stable are epoxides? A novel synthesis of epothilone B" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION., vol. 39, no. 3, 4 February 2000 (2000-02-04), pages 581-583, XP002156413 VERLAG CHEMIE. WEINHEIM., DE ISSN: 0570-0833 the whole document	1-7

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/US 00/20064

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9719086 A	29-05-1997	DE 19542986 A	22-05-1997
		DE 19639456 A	26-03-1998
		EP 0873341 A	28-10-1998
		EP 0903348 A	24-03-1999
		JP 2000500757 T	25-01-2000